REPURPOSING TO SPEED CHEMICAL AND BIOLOGICAL MEDICAL COUNTERMEASURE DISCOVERY AND DEVELOPMENT

Design And Synthesis Of Diketopiperazine (dkp) As Shuttles For Therapeutics Across The Blood-brain Barrier

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Nerve agents are organophosphorus (OP) containing compounds, which are primarily found in chemical warfare agents and pesticides. OP exposure results in the irreversible inhibition of acetylcholinesterase (AChE) by phosphorylation of serine in the active site, resulting in the buildup of the neurotransmitter acetylcholine (ACh). AChE is responsible for proper ACh signaling in the cholinergic system, and inhibition can cause a number of symptoms including loss of consciousness, paralysis, seizures, respiratory failure, and death. Current treatment for OP exposure involves the use of pralidoxime (2-PAM), which acts by nucleophilic attack on the phosphorylated serine in the AChE active site, subsequently freeing the serine and reactivating AChE. Unfortunately, treatment only works on the peripheral nervous system as 2-PAM cannot cross the blood-brain barrier (BBB), meaning damage to the central nervous system (CNS) is permanent. This results in the need to develop a system to efficiently deliver oxime AChE reactivators across the BBB.

We propose the use of peptoid-based diketopiperazines (DKPs) as a means to deliver AChE reactivators across the BBB. Traditional DKPs are typically cyclic dipeptides known to cross the BBB, however, they degrade rapidly in vivo. In our system, this is solved with the use of peptoid-based DKPs, which help boost the stability 10,000-fold towards proteolytic degradation. Another problem with AChE reactivators is that they include a positive charge; the DKPs are designed as such so that they can fold and mask the charge of the therapeutic. Upon choosing this suitable shuttle, a linker was chosen in order to allow for release of the therapeutic. The lifetime of these linkers needs to be long enough to pass the BBB but short enough to release the therapeutic in a timely manner. As such, linkers consisting of amides and esters were chosen in order to undergo proteolytic cleavage and the kinetics of cleavage were characterized. An additional point of consideration is the attachment of the linker to the therapeutic itself. Several types of linkers and positions on the therapeutics were analyzed in order to ensure that reactivation of AChE occurs. This work aims to elaborate on 1. Shuttles that can mask therapeutic charge and successfully pass the BBB; and 2. Linkers that can release the therapeutic in an appropriate time frame while maintaining AChE reactivation.